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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	12

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/720,923	WENGER ET AL.
	Examiner	Art Unit
	Samuel W Liu	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b)

Status

1)☒ Responsive to communication(s) filed on *07 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-21* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed 7 February 2003 (Paper No. 11) as to cancellation of claims 8-14, addition of claims 15-21, and Applicant's request for extension of time of one months filed 7 February 2003 (Paper No. 10) have been entered. The following is applicable to the pending claims 15-21.

Note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 15-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites "(N-R) aa"; the recitation is unclear as to what is aa refers because the it has not been defined in the specification, and as to what is the meaning of "N-R", which should be spelled out for the first instance in the claims. Does "N-R" mean "Asn-Arg"? The specification at page 7, line 11, would appear to indicate "R" is "$> CH_3$" rather than "Arg". The dependent claims are also rejected.

Claim 16 is indefinite as to whether or not the recitation "(R) Val" refers to the side chain group "R" (i.e., R group) is linked to valine side chain or the R group is conjugated to α-N of the valine residue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The Claims 15-16 and 18 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Steiner J. P. et al. (US Pat. No. 6444643).

Steiner et al. teach a cyclosporin compound that reads on the structure set forth in Claim 15 of the instant application, *i.e.*, positions 1 through 11 have (4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine (MeBmt), α-aminobutyric acid (Abu), sarcosine (Sar), an amino acid residue with N-alkylation (see column 11, line 18), Val, MeLeu, Ala, D-Ala, MeLeu, MeLeu and MeVal, respectively (see formula IV and column 10), as applied to claims 15 of the instant application.

Also, Steiner et al. disclose that the position 4 residue of the cyclosporin structure undergoes alkylation, e.g., C1-C9 branched chain alkyl which meets limitation "(R)Val where R > CH_3 and R < $C_{10}H_2$" set forth in the application claim; the Steiner teaching is thus applied to claim 16 of the instant application.

Further, Steiner et al. teach formulation of the claimed cyclosporin into the pharmaceutical composition (see columns 5-6), as applied to claims 18-19 of the instant application. Since that claims 20-21 refer to intended use of the claimed cyclosporin, claims 20-21 are also included in the rejection.

Therefore, the disclosure of Steiner et al. anticipates the subject matter of Claims 15-16 and 18-21 of the current application.

Response to the rejection under 35 USC 102

The response filed 7 February 2003 asserts that the Steiner et al. patent does not anticipates the composition of present application as the patent does not teach that the number 4 position (i.e., Z residue of the current disclosure) is not simply methylated amino acid but rather an amino acid having an N-alkyl group greater than methyl (see page 7, the six paragraph). Steiner et al. teach N-alkylation of Valine at the position 4 (see the statement *supra*) which would include ethylation. Thus, the argument is not persuasive. Also, the response argues that the Steiner patent does not teach the disclosed cyclosporin has anti-HIV activity; thus it cannot be applied to the application claims (see page 8, the third paragraph). The applicants' argument is found unpersuasive because the recited activity of treating and preventing AIDS refers to an intended use for the pharmaceutical composition comprising the cyclosporin and there is no

patentable weight associated with the use of the composition which has identical structure. Identical structure would be anticipated to result in identical biological activity.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15-21 are rejected under 35 U.S.C. 103(a) as being obvious over Ko, S. Y. et al. (US Pat No. 5767069) taken with Steiner, J. P. et al (US Pat. No. 6444643).

Ko et al. teach a synthesized cyclosporin compound in which at positions 1 through 11 have (4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine (MeBmt), α-aminobutyric acid (Abu), sarcosine (Sar), an N-alkyl (methyl) modified amino acid (MeIle), Val, MeLeu, Ala, D-Ala, MeLeu, MeLeu and MeVal, respectively (see Claim 1, column 5and formula I), as applied to claim 1 of the instant application.

Also, Ko et al. teach a pharmaceutical composition comprising the cyclosporin as set forth above (see Claim 4), as applied to claims 19-20 of the current application.

Further, Ko (Us Pat. No. 5767069) et al. teach an active cyclosporin compound for anti-HIV *i.e.*, treatment of AIDS (see example 12, Claim 4, columns 3 and 4, and column 5, lines 1-6), as applied to claims 20-21 of the instant application.

Ko (US Pat No. 5767069) et al. do not expressly teach amino acid residue at position 4 of the cyclosporin is alkylated (*e.g.*, ethyl group > methyl group).

Steiner et al. teach a cyclosporin compound that reads on the structure set forth in Claim 15 of the instant application, *i.e.*, positions 1 through 11 have (4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine (MeBmt), α-aminobutyric acid (Abu), sarcosine (Sar), an amino acid residue with N-alkylation (see column 11, line 18), Val, MeLeu, Ala, D-Ala, MeLeu, MeLeu and MeVal, respectively (see formula IV and column 10), as applied to claims 15 of the instant application. Also, Steiner et al. teach that the position 4 residue of the cyclosporin structure undergoes alkylation, e.g., N-alkylated $[Val]^4$, as applied to claims 16 and 17 of the current application.

One of ordinary skill in the art would have combined the teachings of Ko et al. and Steiner, et al. because the two references provide very similar cyclosporin structures and Steiner et al. teach N-alkylation at amino acid position 4, and because Ko et al. teach that active

compounds have structure differing from that of cyclosporin specifically at the 4 and/or 5 positions (see column 5, lines 7-9) and teach that amino acid which is N-alkylated is valine, and preferably the hydrogen of the imino group of valine residue is replaced by a non-branched C_{1-6} alkyl group, e.g., ethyl, which are biologically active (see column 5, lines 19-26).

In addition, when combined there would have been the following advantages: (*a*) various modifications of position 4 of cyclosporin retains biological activities of the modified compounds as taught by Ko et al. (see column 5, lines 7-9); and (*b*) derivatives and analogue of cyclosporin, e.g. N-alkylated Valine at position 4, lack immunosuppressive effect (i.e., *non-immunosuppressive*), which is an important factor for therapeutic use of the synthesized nonimmunosuppressive cyclosporin variant in treatment of disorder state, e.g. AIDS as taught by Steiner et al. (see column 11, lines 16-23).

Given the above motivation one of ordinary skill in the art would have combined the above reference teachings and would have successfully arrive the invention as to development of a therapeutic composition for treating HIV-infection comprising modification at position 4 of the cyclosporin compound, *e.g.*, N-alkylated Valine including N-ethyl Valine and testing for their anti-HIV activities, which are based on the cyclosporin disclosed in the art. Thus, the claimed invention was *prima facie* obvious to make and use at the time it was made.

Response to the rejection under 35 USC 103(a)

The response filed 7 February 2003 asserts that the combination of teachings by Ko et al. and Steiner et al. does not constitute an obvious art over the current disclosure regarding N-alkyl (i.e., N-ethyl) Valine which has anti-HIV activity and lower immunosuppressive activity (see the

bridging pages 8-9). The applicants' argument is not persuasive because Steiner et al. teach N-alkylated Valine that is non-immunosuppressive, and Ko et al. teach that active compounds have structure differing from that of cyclosporin specifically at the 4 and/or 5 positions and that amino acid which is N-alkylated is Valine residue, and preferably the hydrogen of the imino group of valine residue is replaced by a non-branched C_{1-6} alkyl group, e.g., ethyl, which is anti HIV active (see the statement *supra*).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher

Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Christopher S.F. Low

Samuel Wei Liu, Ph.D.

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March 31, 2003